

Application No. 10/798,131  
Docket No. 5677-211  
Third Supplemental Preliminary Amendment

**In the Specification:**

On page 50, rewrite Example 12 as follows and delete inserted Figure 1b:

Preparation of (+)-Catechin (4 $\alpha$ →8)-(-)-epicatechin

Tetra-*O*-benzyl-(+)-catechin-(4 $\alpha$ →8)-(-)-epicatechin prepared in Example 11 (50 mg) was dissolved in methanol (10 mL) and degassed by blowing argon for 10 min. 30% Palladium-charcoal (30 mg) was added and hydrogenolysis conducted at 45 psi for 3 hours. The solution was filtered through Celite which was washed with methanol. The combined filtrate and washings were evaporated and the residue was dissolved in water, then lyophilized to provide a quantitative yield of the dimer as an off-white solid. For the NMR spectrum the Hs comprising the upper monomer of the dimer are designated A and the Hs comprising the lower monomer of the dimer are designated B. <sup>1</sup>H NMR (CDCl<sub>3</sub>:d<sub>4</sub>-methanol, 9:1)  $\delta$ <sub>H</sub> 7.21 (1H, bs, A-2'), 7.04 (1H, bs, B-2'), 6.95-6.75 (2H, m, A-5', B-5'), 6.62 (1H, m, A-6'), 6.45 (1H, m, B-6'), 6.20 (1H, m, B-6'), 6.05 (1H, m, B-6'), 5.89 (2H, m, A-6, A-8), 4.98 (1H, m, B-2), 4.85 (1H, m, B-2), 4.42-4.25 (3H, m, A-4, A-3, A-2), 3.05-2.62 (2H, m, B-4). ~~Figure 1b is a representative HPLC separation of the (+)-catechin (4 $\alpha$ →8)-(-)-epicatechin prepared above.~~

On page 53, rewrite Example 16 as follows and delete inserted Figure 1a and inserted Figure 2:

Preparation of (-)-Epicatechin-(4 $\beta$ →8)-(-)-epicatechin

Tetra-*O*-(-)-epicatechin (4 $\beta$ →8)-(-)-epicatechin prepared in Example 15 (40 mg, 0.043 mmol) was dissolved in 8 mL methanol and degassed by blowing argon for 10 min. To the solution, 25 mg of 30% palladium-charcoal was added and the mixture hydrogenolyzed at 45 psi for 3 hours. The solution was filtered through Celite followed by washing with 25 mL methanol. The combined filtrate and washing were evaporated and the residue dissolved in water. Lyophilization provided 23 mg of an off-white powder. HPLC analysis (~~Figure 1A~~) revealed the presence of 18% monomer, 45% dimer, 25% trimer and 8% tetramer. ~~The <sup>1</sup>H NMR spectrum is shown in Figure 2.~~

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On page 55, rewrite Example 20 as follows and delete inserted Figure 3:

Preparation of Tetra-*O*-benzyl-(+)-catechin-

(4 $\alpha$ →8)-3-acetyl-(+)-catechin-(4 $\alpha$ →8)-pentaacetyl (-)-epicatechin

To a solution of 3-acetyl-(+)-catechin-(4 $\alpha$ →8)-pentaacetyl(-)-epicatechin prepared by Example 14 (100 mg, 0.068 mmol) and 4 $\beta$  acetoxyl tetra-*O*-benzyl-(+)-catechin prepared by Example 6 (334 mg, 2 eq) in THF (7 mL) and methylene chloride (7 mL), 161 mg of LiI was added. The solution was refluxed for 24 hours, followed by partition between ethyl acetate and water (25 mL each). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent evaporated. The residue was subjected to silica gel chromatography where elution with ethyl acetate-methylene chloride (1:1, v/v) provided a brownish white solid (100 mg, 28%) after the evaporation of the solvent. The resulting <sup>1</sup>H NMR is shown in Figure 3. MS (FAB, *m/z*) 1482 (M+H)<sup>+</sup>, 1148, 1042, 962, 920, 650.

On page 55, rewrite Example 21 as follows and delete inserted Figure 4:

Preparation of Tetra-*O*-benzyl-(+)-catechin-(4 $\alpha$ →8)

-pentaacetyl-(+)-catechin-(4 $\alpha$ →8)-pentaacetyl (-)-epicatechin

Tetra-*O*-benzyl-(+)-catechin-(4 $\alpha$ →8)-3-acetyl-(+)-catechin-(4 $\alpha$ →8)-pentaacetyl (-)-epicatechin prepared by Example 20 (100 mg, 0.068 mmol) was stirred in dry pyridine (2 mL) and acetic anhydride (1 mL) under argon for 24 hours. The solution was then partitioned between 1N HCl and ethyl acetate (25 mL each), the organic layer was washed with 5% NaHCO<sub>3</sub>, saturated NaCl and dried over MgSO<sub>4</sub>. Evaporation of the solvent provided an oily residue which was subjected to silica gel chromatography where elution with 10% ethyl acetate in methylene chloride provided a white powder (70 mg, 61%) after evaporation of the solvent. The resulting <sup>1</sup>H NMR is shown in Figure 4.

On page 56, rewrite Example 22 and delete inserted Figure 5:

Preparation of 3 Acetyl-(+)-catechin-(4 $\alpha$ →8)

-pentaacetyl-(+)-catechin-(4 $\alpha$ →8)-pentaacetyl (-)-epicatechin

Tetra-*O*-benzyl-(+)-catechin-(4 $\alpha$ →8)-pentaacetyl-(+)-catechin-(4 $\alpha$ →8)-pentaacetyl (-)-epicatechin prepared in Example 21 (50 mg) was dissolved in degassed ethyl acetate-methanol (3

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mL each) and hydrogenolysed for 4 hours in the presence of 30% palladium-charcoal (30 mg) at 45 psi. Removal of the catalyst via filtration through Celite and evaporation provided the title compound as a pale brown powder (35 mg, 91%). ~~The resulting  $^1\text{H}$  NMR is shown in Figure 5.~~

On page 57, rewrite lines 1 to 5 as follows and delete inserted Figure 6:  
mixture refluxed for 24 hours. The solution was partitioned between ethyl acetate and water (25 mL each) and the organic layer dried over  $\text{MgSO}_4$ . The solvent was evaporated and the residue subjected to silica gel chromatography where elution with ethyl acetate-methylene chloride (1:1, v/v) provided a

white powder (35 mg, 30%) after evaporation of the solvent. ~~The resulting  $^1\text{H}$  NMR is shown in Figure 6.~~

MS (FAB,  $m/z$ ) 1588 ( $\text{M} + \text{H}$ )<sup>+</sup>, 1255, 772, 648, 607, 560.

On page 60, at lines 1-5, rewrite the text as follows and delete inserted Figure 7:  
The assignment of the correct absolute configuration was tested by calculation of the Flack 'x' parameter. This parameter was indistinguishable from zero, indicating the correct configuration was assigned. A test refinement of the inverted configuration resulted in a Flack 'x' parameter value of 0.95(5) and a significant increase in the R factors, both indicating that the assignment was correct. ~~The final model for 8-bromo-tetra-O-benzyl-( $-$ )-epicatechin is shown in Figure 7.~~